Zirconium(IV) chloride-catalyzed synthesis of 1,5-benzodiazepine derivatives

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Abstract: Zirconium tetrachloride efficiently catalyzes the cyclocondensation reaction of *o*-phenylenediamine and a ketone in refluxing 1,2-dichloroethane to afford the corresponding 2,3-dihydro-1*H*-1,5-benzodiazepine in high yield. The formation of specific regioisomers and their structural elucidation are reported for the first time.

Key words: zirconium tetrachloride, *o*-phenylenediamines, ketones, 1,5-benzodiazepines, ^{1}H NMR, regioisomers.

Résumé : Le tétrachlorure de zirconium catalyse d'une façon efficace la réaction de cyclocondensation de l'*o*-phénylènediamine avec les cétones, dans du 1,2-dichloroéthane au reflux, pour conduire à la formation des 2,3-dihydro-1*H*-1,5-benzodiazépines, avec un rendement élevé. On rapporte pour la première fois la formation de régioisomères spécifiques ainsi que l'élucidation de leurs structures.

Mots-clés : tétrachlorure de zirconium, *o*-phénylènediamines, cétones, 1,5-benzodiazépines, RMN du ^{1}H, régioisomères.

[Traduit par la Rédaction]

Introduction

Benzodiazepines are important pharmaceutical compounds that are frequently used as prescribed drugs for combating central nervous system (CNS)-related diseases mainly because of their anticonvulsant, hypnotic, and other properties (1, 2). They are also used as intermediates in the manufacture of commercially important cationic dyes for acrylic fibers (3) and also used as starting materials for the preparation of fused ring compounds such as triazolo- (4), oxadiazolo- (5), oxazino- (6), or furano-benzodiazepines (7). More interestingly, the related diazapines showed unusual and novel pharmacological activity as HIV-1 reverse transcriptase inhibitors, as evidenced by niverperin (8). Because of their versatile biological activity and commercial utility, the synthesis of these compounds has acquired greater attention in synthetic organic chemistry and led to the development of new synthetic strategies. Generally, these compounds are prepared by cyclocondensation of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds (9), β-haloketones (10), or ketones, involving combinations of Lewis acids and transition-metal salts like BF_3-etherate (11), $NaBH_4$ (12), polyphosphoric acid or (SiO_2) (13), $MgO/POCl_3$ (14), $Yb(OTf)_3$ (15), and Al_2O_3/P_2O_5 under microwave conditions (16). However, many of these methods suffer from drawbacks, such as drastic reaction conditions, cumbersome workup procedures, low yields, and co-occurrence of several side reactions. Therefore, there is still a need to develop new catalytic methods for the synthesis of these biologically active compounds.

Recently, zirconium(IV) chloride has received considerable attention as an efficient Lewis acid catalyst for various organic transformations such as Biginelli's reaction (17), electrophilic amination of activated arenes (18), thioacetylation of acetals, (19) deoxygenation of heterocyclic-*N*-oxides (20), reduction of nitro-compounds (21), and conversion of carbonyl compounds to 1,3-oxathiolanes (22). To continue our interest in zirconium(IV) chloride as a catalyst for novel synthetic methodologies (17, 23), we envisaged its use and effect in the cyclocondensation of ketones with *o*-phenylenediamine.

Results and discussion

In this paper, we wish to present the results of a facile one-pot method for the synthesis of 1,5-benzodiazepines catalysed by $ZrCl_4$,and also to report, for the first time, the unequivocal structure elucidation of the regioisomers formed in this reaction. Typically, 5 mmols of *o*-phenylenediamine were reacted with 10 mmols of ketone in 1,2-dichloroethane under refluxing condition for 30–180 min (Scheme 1). The cyclocondensation is catalyzed by 10 mol% of $ZrCl_4$ to afford the corresponding 1,5-benzodiazepine derivatives in good to excellent yields. The effects of different solvents such as acetonitrile, tetrahydrofuran, ethanol, dichloromethane, and 1,2-dichloroethane on the yield of 1,5-benzodiazepine in presence of 10 mol% of catalyst was studied, and it was observed that 1,2-dichloroethane was the solvent of choice in terms of yield and reaction time. Regarding the optimum quantity of the catalyst, it was found that 10 mol% of $ZrCl_4$ is necessary to promote the reaction. However, no reaction was observed in the absence of the catalyst,

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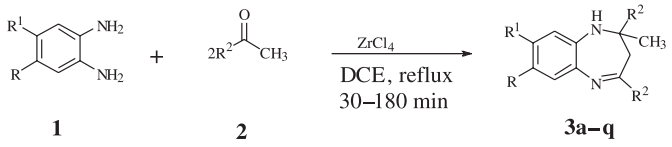
Table 1. Zirconium(IV) chloride-catalyzed formation of 1,5-benzodiazepines.

Product[a]	R	R^1	R^2	Yield (%)[b]	Time (min)	Mp (°C)[b]
3a	H	H	C_6H_5	90	30	107–108
3b	H	H	4-(Me)–C_6H_4	96	60	88–89
3c	H	H	4-(Cl)–C_6H_4	94	55	133–135
3d	H	H	4-(Br)–C_6H_4	97	50	145–146
3e	H	H	4-(OMe)–C_6H_4	89	65	120–121
3f	H	H	4-(NO_2)–C_6H_4	92	60	132–133
3g	H	H	CH_3	96	30	119–120
3h	H	H	CH_2–CH–$(CH_3)_2$	88	90	117–118
3i	CH_3	CH_3	C_6H_5	92	45	118–120
3j	CH_3	CH_3	4-(NO_2)–C_6H_4	97	60	127–128
3k	CH_3	CH_3	4-(Cl)–C_6H_4	92	45	146–147
3l	CH_3	CH_3	4-(Me)–C_6H_4	95	60	120–122
3m	NO_2	H	C_6H_5	70	180	144–145
3n	NO_2	H	4-(Cl)–C_6H_4	72	180	173–174
3o	NO_2	H	4-(Br)–C_6H_4	80	180	160–162
3p	OCH_3	H	C_6H_5	85	150	120–121
3q	OCH_3	H	4-(Cl)–C_6H_4	85	150	115–118

[a]All products were characterized by ^{1}H NMR, IR, and mass spectroscopy.
[b]Isolated and unoptimized yields, and melting points are uncorrected.

Scheme 1.



1 **2** **3a–q**

even after prolonged reaction time (>18 h), under the present reaction conditions.

Optimizing the reaction conditions, we extended this procedure to a number of 1,5-bezodiazepine derivatives, using $ZrCl_4$ (10 mol%) in 1,2-dichloroethane at reflux temperature. The results summarized in Table 1 indicate the scope and generality of the reaction with respect to the examples described therein. As shown in Table 1, the reaction of acetone with *o*-phenylenediamine in the presence of $ZrCl_4$ afforded 2,2,4-trimethyl-2,3-dihydro-1*H*-benzodiazepine (Table 1, entry 7) in 96% yield. Acetophenone reacted with *o*-phenylenediamine under similar reaction conditions to yield 2-methyl-2,4-diphenyl-2,3-dihydro-1,5-bezodiazepine (Table 1, entry 1) in 90% yield. The cyclocondensation of *o*-phenylenediamine with *para*-substituted acetophenones and aliphatic ketones afforded the corresponding 1,5-benzodiazepine derivatives in good yields (88%–97%), indicating that the substitution on a ketone substrate has little effect on the yield (Table 1, **3a–i**). The cyclocondensation reaction may be proceeding via an intramolecular imine–enamine cyclization, promoted by $ZrCl_4$, as depicted in Scheme 2 (13). It may be presumed that the carbonyl group of the ketone coordinates with $ZrCl_4$, forming a complex **C** (17) for which we have no evidence, yet its formulation seems reasonable. The amine of *o*-phenylenediamine attacks the carbonyl group of the ketone, giving the intermediate dimine **A**. Then, 1,3-shift of the hydrogen attached to the methyl group occurs to form an isomeric enamine **B**, which on cyclization affords the seven-membered ring.

4-Substituted *o*-phenelenediamines were reacted with acetone, as well as acetophenone, to give the corresponding 1,5-benzodiazapine derivatives. Although the formation of 7- or 8-substituted 1,5-benzodiazepines from the corresponding 4-substituted *o*-phenylenediamines (e.g., 4-chloro, 4-nitro, 4-methyl, and 4-benzoyl) and acetone, acetophenone, or cyclohexanone was previously reported, the structure confirmation of the products has not been reported, and there exists ambiguity of the regioisomers (24). Similar to this is the case of the formation of a mixture of regioisomers in the ratio of 60:40, corresponding to 7- and 8- substituted 1,5-benzodiazapine derivatives obtained from 4-chloro and 4-benzoyl *o*-phenolenediamines and acetone (25). At this point, it is noteworthy to mention that the $ZrCl_4$-catalyzed reaction between 4-nitro, 4-methoxy *o*-phenylenediamine and the acetophenone derivative led to the formation of specific regioisomer in good yields (**3m–q**). The formation of regioisomers is in accordance with the mechanism (Scheme 2) proposed by Jung and co-workers (13), in which the intramolecular imine–enamine cyclization is favored by the presence of an electron-withdrawing group (NO_2) *para* to imine moiety, and *para* to enamine moiety in case of an electron-donating group (OCH_3). The intermediate formed in this reaction does not require the activation of amino-functionality, and as a result, the electronic nature of the substituent may not have significant effect on the yield; however, it affected the nature of cyclization, leading to the formation of specific regioisomers. We report detailed structural elucidation of the regioisomers (**3m–q**), using ^{1}H NMR spectroscopic data and the chemical shifts of the diagnostic protons along with the coupling constants, in Table 2 for the first time.

In 2-methyl-7-nitro-2,4-di(4′-chlorophenyl)-2,3-dihydro-1*H*-1,5-benz-odiazepine (**3n**, Fig. 1*a*), the *meta* coupled doublet at δ 8.18 ppm (J = 2.4 Hz) is assigned to a proton (6-H) *ortho* to the imine nitrogen of benzodiazepines, which is in the downfield region compared with the *ortho* coupled doublet at δ 6.76 ppm (9-H) (J = 9.0 Hz), which is *ortho* to the amine nitrogen. The *ortho* and *meta* coupled doublet of doublet at δ 7.89 ppm (J = 9.0 and 2.4 Hz) is assigned to 8-H.

Scheme 2.

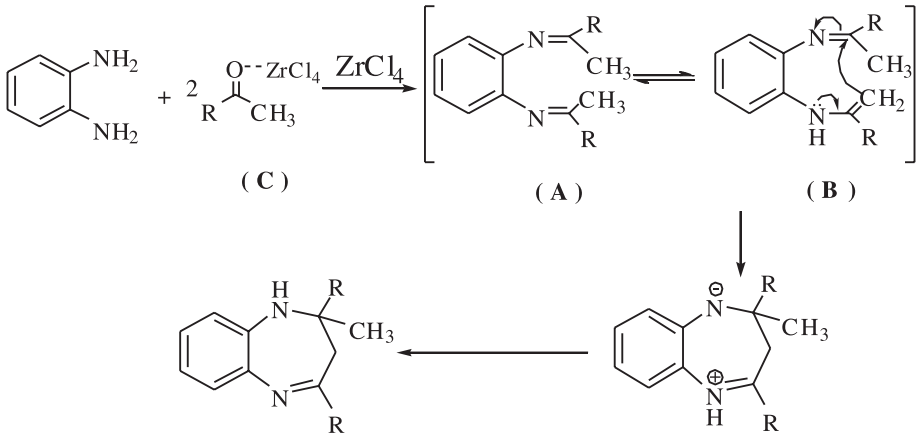


Table 2. Selected ^{1}H NMR chemical shifts of compounds **3m**, **3n**, **3o**, **3p**, **3q**, and **3r**.

Compound	$C_{6\text{-H}}$	$C_{8\text{-H/7-H}}$	$C_{9\text{-H}}$
3m	δ 8.24	δ 7.92	δ 6.76
	d (*J* = 2.5 Hz)	dd (*J* = 8.5 and 2.5 Hz)	d (*J* = 8.4 Hz)
3n	δ 8.18	δ 7.89	δ 6.76
	d (*J* = 2.4 Hz)	dd (*J* = 9.0 and 2.4 Hz)	d (*J* = 9.0 Hz)
3o	δ 8.26	δ 7.95	δ 6.81
	d (*J* = 2.4 Hz)	dd (*J* = 8.9 and 2.4 Hz)	d (*J* = 8.9 Hz)
3p	δ 7.19 d	δ 6.52	δ 6.28
	Merged[a]	dd (*J* = 8.7 and 2.2 Hz)	d (*J* = 2.2 Hz)
3q	δ 7.20 d	δ 6.54	δ 6.26
	Merged[a]	dd (*J* = 8.7 and 2.3 Hz)	d (*J* = 2.3 Hz)
3r (*N*-methyl)	δ 6.90	δ 6.68	δ 6.76
	d (*J* = 9.0 Hz)	dd (*J* = 9.0 and 3.0 Hz)	d (*J* = 3.0 Hz)

[a]Merged with the ab quartet of other aromatic protons.

The same analogy is applicable to 2-methyl-7-nitro-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3m**) and 2-methyl-7-nitro-2,4-di(4′-bromophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**3o**). However, in case of methoxy substituted benzodiazepines, namely 2-methyl-8-methoxy-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**3p**) and 2-methyl-8-methoxy-2,4-di(4′-chlorophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**3q**) (Table 1), the *meta* coupled doublet (9-H) at δ 6.28 ppm (*J* = 2.2 Hz) is in the most shielded region, and the *ortho*-coupled proton (6-H) signal is merged with the other aromatic-proton signals in the region of δ 7.1–7.2 ppm. The doublet of doublet at δ 6.52 ppm (7-H) with a coupling constant of 8.7 and 2.2 Hz, respectively, is assigned to *ortho* and *meta* couplings of 6-H and 9-H protons. This clearly indicates that the shielded proton in this derivative is *ortho* to the amine nitrogen. Therefore, structure **3p** has been assigned for the methoxy-substituted benzodiazapine derivative (Fig. 1*b*). This is further confirmed by converting compound **3p** into its *N*-methyl derivative (1,2-dimethyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepin-8-yl methyl ether (**3r**)) using dimethyl sulfate under phase transfer catalysis (PTC) conditions (26). The ^{1}H NMR spectrum of the methylated compound **3r** (Fig. 1*b*) revealed the presence of a *meta*-coupled doublet at δ 6.76 ppm (*J* = 3.0 Hz), *ortho*-coupled doublet at δ 6.90 ppm (*J* = 9.0 Hz), and doublet of doublet at δ 6.68 ppm (*J* = 9.0 and 3.0 Hz) that are assigned to 9-H, 6-H, and 7-H, respectively.

To the best of our knowledge, 2-methyl-8-methoxy-2,4-di(4′-chlorophenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**3q**) is reported for the first time, and the structures of the regioisomers have been unequivocally assigned, based on IR, NMR, and mass spectral data, and finally confirmed by X-ray crystallographic analysis.[2]

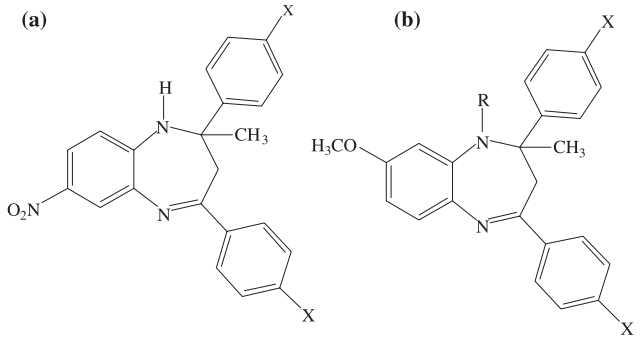
In conclusion, the results reveal that $ZrCl_4$ has proved to be an effective catalyst for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines. This protocol offers several advantages, such as selectivity, high yields, shorter reaction times, and simple workup procedure. Moreover, the interesting outcome of the present study is the isolation of the specific regioisomers **3m**–**q** in high yields, and their structures have been unequivocally characterized by spectroscopic data for the first time.

Experimental

NMR, spectra were recorded on Gemini 200, 300, and 400 MHz and Avance 600 spectrometers in $CDCl_3$, using TMS as internal standard. IR spectra were recorded on a

[2]G.Y.S.K. Swamy, K. Ravikumar, V.V.N. Reddy, and K.S. Reddy. Manuscript in preparation.

Fig. 1.



3m: X = H
3n: X = Cl
3o: X = Br

3p: R = X = H
3q: R = H, X = Cl
3r: R = CH_3, X = H

Nicolet 740 FTIR spectrometer, and Mass spectra were recorded on a VG Micro Mass 7070H. The melting points were determined in open glass capillaries on a Metler FP 51 melting point apparatus and are uncorrected. All reactions were carried out using reagent-grade solvents, and the reagents were purchased from local suppliers except $ZrCl_4$, which was purchased from Merck Limited, Mumbai.

General procedure for the $ZrCl_4$-catalyzed synthesis of 1,5-benzodiazepines (3)

A mixture, containing *o*-phenylenediamine (5 mmol), ketone (10 mmol), and $ZrCl_4$ (10 mol%) in 1,2-dichloroethane (15 mL), was refluxed for an appropriate period of time, as mentioned in Table 1. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature and washed with water (3 × 10 mL). The organic layer was dried over anhyd. Na_2SO_4, and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel (100–200 mesh), using hexane – ethyl acetate (98:2) as an eluent to afford the pure products.

Spectroscopic data

*2-Methyl-7-nitro-2,4-diphenyl-2,3-dihydro-1*H-*1,5-benzodiazepine (3m)*

Yellow solid; mp 144–145 °C. IR (KBr) (cm^{-1}): 3300, 1651. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.80 (s, 3H, CH_3), 3.05–3.37 (dd, 2H, CH_2, *J* = 12.6 Hz), 4.40 (br s, 1H, NH, D_2O exchangeable), 6.76 (d, 1H, ArH, *J* = 8.4 Hz), 7.1–7.4 (m, 8H, ArH), 7.6 (d, 2H, ArH, *J* = 6.74 Hz), 7.92 (dd, 1H, ArH, *J* = 8.5 and 2.5 Hz), 8.24 (d, 1H, ArH, *J* = 2.50 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.7, 44.2, 69.0, 119.0, 122.3, 125.0, 127.0, 127.4, 128.1, 128.4, 130.0, 134.6, 139.4, 140.1, 144.4, 146.0, 167.2. MS–FAB *m/z* (%): 357 ($[M]^+$, 30), 345 (10), 282 (20), 241 (100), 194 (10), 130 (25), 119 (30), 78 (10), 57 (50). HR-ESIMS: ($[MH]^+$) *m/z* calcd. for $C_{22}H_{20}N_3O_2$: 358.1555; found: 358.1566.

*2-Methyl-7-nitro-2,4-di(4′-chlorophenyl)-2,3-dihydro-1*H-*1,5-benzodiazepine (3n)*

Yellow solid; mp 173–174 °C. IR (KBr) (cm^{-1}): 3500, 1600, 1550, 1300. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.73 (s, 3H, CH_3), 2.92–3.35 (dd, 2H, CH_2, *J* = 13.6 Hz), 4.43 (br s, 1H, NH, D_2O exchangeable), 6.76 (d, 1H, ArH, *J* = 9.0 Hz), 7.13 (d, 2H, ArH, *J* = 9.2 Hz), 7.18 (d, 2H, ArH, *J* = 8.0 Hz), 7.21 (d, 2H, ArH, *J* = 8.5 Hz), 7.41 (d, 2H, ArH, *J* = 8.2 Hz), 7.89 (dd, 1H, ArH, *J* = 9.0 and 2.4 Hz), 8.18(d, 1H, ArH, *J* = 2.4Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1, 43.9, 69.1, 119.2, 122.5, 126.7, 127.4, 128.3, 128.4, 128.6, 133.5, 134.7, 136.7, 137.6, 140.7, 143.9, 144.3, 165.7. MS–FAB *m/z* (%): 426 ($[M + H]^+$, 15), 391 (25), 274 (15), 154 (55), 136 (45), 107 (28), 91 (60), 77 (50), 57 (100). HR-ESIMS: ($[MNa]^+$) *m/z* calcd. for $C_{22}H_{18}N_3O_2Cl_2$: 448.0595; found: 448.0595.

*2-Methyl-7-nitro-2,4-di(4′-bromophenyl)-2,3-dihydro-1*H-*1,5-benzodiazepine (3o)*

Yellow solid; mp 160–162 °C. IR (KBr) (cm^{-1}): 3500, 1500, 1550, 1310. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3H, CH_3), 2.94–3.35 (dd, 2H, CH_2, *J* = 13.6 Hz), 4.50 (br s, 1H, NH, D_2O exchangeable), 6.81 (d, 1H, ArH, *J* = 8.9 Hz), 7.2–7.43 (m, 8H, ArH), 7.95 (dd, 1H, ArH, *J* = 8.9 and 2.4 Hz), 8.26 (d, 1H, ArH, *J* = 2.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 31.0, 43.9, 69.2, 119.3, 121.7, 122.6, 125.2, 127.1, 127.3, 128.5, 131.5, 131.6, 134.8, 138.1, 140.8, 143.8, 144.8, 165.8. MS–FAB *m/z* (%): 516 ($[MH + 2]^+$, 80), 391 (45), 319 (40), 154 (100), 136 (85). HR-ESIMS: ($[MH]^+$) *m/z* calcd. for $C_{22}H_{18}N_3O_2Br_2$: 513.9765; found: 513.9780.

*2-Methyl-8-methoxy-2,4-diphenyl-2,3-dihydro-1*H-*1,5-benzodiazepine (3p)*

Yellow solid; mp 120–121 °C. IR (KBr) (cm^{-1}): 3350, 2950, 1620, 1490, 1250. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 3H, CH_3), 2.94–3.15 (dd, 2H, CH_2, *J* = 12.87 Hz), 3.54 (br s, 1H, NH, D_2O exchangeable), 3.80 (s, 3H, OCH_3), 6.28 (d, 1H, ArH, *J* = 2.2 Hz), 6.52 (dd, 1H, ArH, *J* = 8.7 and 2.2 Hz), 7.10–7.25 (m, 5H, ArH), 7.51 (m, 6H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.1, 43.6, 55.4, 71.5, 105.6, 106.7, 125.4, 126.9, 127.0, 128.0, 128.3, 129.3, 130.8, 133.0, 139.5, 140.1, 147.7, 158.2, 165.1. MS–FAB *m/z* (%): 343 ($[M + H]^+$, 100), 224 (85), 209 (20), 154 (40), 136 (50). HR-ESIMS: ($[MH]^+$) *m/z* calcd. for $C_{23}H_{23}N_2O$: 343.1810; found: 343.1818.

*2-Methyl-8-methoxy-2,4-di(4′-chlorophenyl)-2,3-dihydro-1*H-*1,5-benzodiazepine (3q)*

Yellow solid; mp 115–118 °C. IR (KBr) (cm^{-1}): 3350, 3000, 1610, 1490, 1230. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 3H, CH_3), 2.85–3.11 (dd, 2H, CH_2, *J* = 13.7 Hz), 3.51(br s, 1H, NH, D_2O exchangeable), 3.80 (s, 3H, OCH_3), 6.26 (d, 1H, ArH, *J* = 2.3 Hz), 6.54 (dd, 1H, ArH, *J* = 8.7 and 2.3 Hz), 7.20 (m, 5H, ArH), 7.51 (d, 4H, ArH, *J* = 9.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2, 43.3, 55.4, 71.1, 105.6, 107.0, 127.0, 128.0, 128.2, 128.3, 130.9, 132.7, 133.0, 135.6, 138.3, 139.0, 145.8, 158.4, 163.3. MS–FAB *m/z* (%): 411 ($[M + H]^+$, 100), 258 (85), 154 (45), 57 (30). HR-ESIMS: ($[MH]^+$) *m/z* calcd. for $C_{23}H_{21}N_2OCl_2$: 411.1030; found: 411.1029.

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